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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/910,920	07/24/2001	Cho-Chou Kuo	41548	2753

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EXAMINER
BASKAR, PADMAVATHI

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 07/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/910,920	KUO ET AL.	
	Examiner	Art Unit	
	Padmavathi v. Baskar	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,8,17 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,8,17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

1. Upon further consideration and review of the application, the final rejection as set forth in the office action dated 2/5/03 is hereby withdrawn.

2. Appellant's brief filed on 10/08/03 is acknowledged. The examiner has withdrawn all the rejections of record and issuing a non-final Office action.

Status of Claims

3. No claims have been amended.

Claims 1-4, 6, 8 and 17-18 are under examination.

Claim Rejections - 35 U.S. C. § 112, first paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4, 6 and 8 are rejected under 35 U.5.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is referred to the interim guidelines on written description published June 15, 1998 in the Federal Register at Volume 63, Number 114, pp 32639-32645 (also available at www.uspto.gov). This is a written description rejection.

Claims 1-4, 6, 8 are drawn to a composition comprising (a) a Chlamydia infection inhibiting amount of a molecule that interacts with one or both mannose-6-phosphate or malmose-6-phosphate receptor; and (b) a pharmaceutically acceptable carrier, diluent or excipient, wherein said molecule is an antibody or mannose-6-phosphate. The antibody specifically binds to mannose-6-phosphate, mannose-6-phosphate receptor, and mannose-6-phosphate binding site.

The specification discloses Chlamydia is an obligate intracellular bacterium and human population is infected with various species *C. pneumoniae, C.trachomatis* and *C.psittaci*. The

extra cellular form consists of infectious elementary bodies (EB), having major outer membrane protein (MOMP) and said MOMP is glycosylated and consists of N-linked high mannose type oligosaccharide. The cell surface receptor for the EB is one that likely interacts with the ligand and appears to have a key role in the bacteria-cell recognition process. The specification discloses that infection of human endothelial cells with *C. pneumoniae* is enhanced by co-culturing endothelial cells with human monocytes and is mediated by monocyte derived soluble factor The specification clearly identifies the enhancing factor as IGF2 (monoclonal antibodies to IGF-2 blocked the infectivity-enhancing factor) and related that Chlamydia infects target cells via IGF-2/Man-6-P receptor. However, the specification fails to teach Chlamydia inhibiting molecule interacts with both Man-6-P and IGF/2 Man-6-P receptor, as it is not known whether binding of IGF-2 or Man-6-P to the IGF/2 Man-6-P receptor affects the C.pneumoniae infection. In addition it is apparent in the art that *Chlamydia* infects cells that lack IGF/2 Man-6-P receptor (see Table 1, Figure 2 of Kuo et al 2002, Microbial Pathogenesis 32:43-48). Further, Raulston 1995 (see page 611 right column through612, left column, first paragraph) Molecular Microbiology 15 (4) 607-616 teach that chlamydia entry and the identification of host cell receptors appears to be multifactorial and varies not only between Chlamydia strains but also according to the host cell-receptors (see page 612, left column, first paragraph). The specification is silent in disclosing whether Chlamydia interacts with both mannose-6-phosphate and mannose-6-phosphate receptor, which is critical to the claimed invention. Further, the specification does not disclose what is the structure of the Chlamydia inhibiting molecule that interacts with both mannose-6-phosphate and Man –6-P receptor. Therefore, the present specification does not meet the guidelines on written description for the claimed compositions because it lacks sufficient disclosure. Therefore, the composition as claimed does not meet the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19

USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she] invented what is claimed." (See Vas-Cath at page 1116). Thus, the specification fails to disclose the composition comprising Chlamydia inhibiting molecule sufficient to allow one skilled in the art to determine that the inventor had possession of the invention as claimed.

6. Claims1-4, 6 and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.
The nature of the disclosed invention is providing compositions comprising Chlamydia inhibiting molecule that interacts with both mannose- 6- phosphate (Man-6-P) and mannose-6-phosphate receptor / IGF-2 receptor (Man-6-P/ IGF-2 receptor). The specification fails to provide an enabling disclosure and guidance regarding how to make and use Chlamydia inhibiting molecule that interacts with Man-6-P and Man-6-P/ IGF-2 receptor of C. *pneumoniae*, *C.trachomatis* and *C.psittaci* as discussed in the written description rejection. The art teaches Chlamydial entry into epithelial cells via mechanisms that still remains to be fully elucidated and (see page 1487, summary and introduction in Journal of Cell Science, 1999, Vol 112, Issue 10 1487-1496) and the identification of host cell receptors appears to be multifactorial and varies not only between Chlamydia strains but also according to the host cell-receptors (see Raulston 1995 page 612, left column, first paragraph). In addition the present specification contemplates that molecules that engage the Man-6-P receptor can be used to prevent binding of the EB to

the cell surface etc. However, the specification fails to provide guidence how to make and use the compositions to inhibit *C. pneumoniae, C.trachomatis* and *C.psittaci* that interact with both Man-6-P and Man-6-P receptor. The specification provides no working examples demonstrating (i.e., guidance) enablement for the claimed composition and the art is devoid of disclosing such composition. Thus, these unknown Chlamydia inhibiting molecules must be considered highly unpredictable, requiring a specific demonstration of efficacy on a case-by-case basis. Thus, the specification fails to provide an enabling disclosure for making and using claimed compositions, absent such demonstration; the invention would require undue experimentation to practice as claimed.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 1-4, 6, 8 and 17-1 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 17 are rejected as being vague for the recitation of "a Chlamydia infection inhibiting amount of a molecule" because the metes and bounds of the term "a Chlamydia infection inhibiting amount " as written are unclear.

Claim Rejections - 35 USC § 102

9 The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1, and 8 are rejected under 35 U.S.C. 102 (b) as being anticipated by Swanson et al 1998, Infection and immunity, Vol 66 (4) 1607-1612.

Claims have been discussed supra.

Swanson et al disclose a composition comprising Human Mannose binding protein (MBP) in a buffer (i., e pharmaceutically acceptable carrier, diluent or excipient, see page 1607, under Human MBP) inhibit infection of Hela cells by *C.trachomatis* (Table 2. abstract. Table 3). Thus the art discloses MBP as Chlamydia inhibiting molecule and binds (i.e. interacts) to ligand high mannose type oligomannose-oligosaccharide associated with glycosylated 40kD MOMP glycoprotein located on the outer surface of elementary body (see abstract, page 1998, under identification of chlamydia proteins that bind to MBP and figure 2 and 4) The prior art anticipated the claimed invention.

13. Claims 1, 2 and 8 are rejected under 35 U.S.C. 102 (b) as being anticipated by Swanson Infect Immun. 1994 Jan, 62(1): 24-8.

Claims have been discussed supra.

Swanson et al disclose a composition comprising high mannose oligosaccharides (Chlamydia inhibiting molecule) that neutralize the *C. pneumoniae, C.trachomatis* and *C.psittaci* infection in Hela cells (Table 4) and thus read on claims 1 and 8. The high mannose interacted with the glycosylated outer membrane protein (MOMP) of Chlamydia trachomatis and thus neutralized the infection. Incubation of [3H] glycan with rabbit immune serum prepared against antigens of whole EB and the MOMP inhibited the attachment and thus rabbit immune serum meets the limitation of claim 2. Thus the prior art anticipated the claimed invention.

14. Claims 1 and 17are rejected under 35 U.S.C. 102 (b) as being anticipated by Su et al, (1996) Proceedings of the National Academy of Sciences USA 93, 11143 - 11148.

Claims have been discussed supra.

Su et al disclose a composition comprising Heparin sulfate in a pharmaceutically acceptable carrier buffer inhibited Chlamydia infection in epithelial cells (Figure 5B). Inhibition of MOMP binding was observed with 1ug/ml Heparin indicating that Heparin interacted with the cell receptor. The teachings of Su et al disclose HS interacts with Man-6-P receptors on the cell (i.e., IGF-2 R, see page 1143, right column) and thereby inhibiting the ligand (MOMP associated glycon) binding to its receptor .The prior art anticipated the claimed invention.

Relevant Prior Art

15. The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

Woods et al Euro J Cell Biol. 1989 Oct; 50(1): 132-43 teach Transferring receptors and cation-independent mannose-6-phosphate receptors deliver their ligands to two distinct subpopulations of multivesicular endosomes. The endosomal subpopulation heavily labeled for M6P-R presumably represent a later endosomal compartment which serves as the junction point where endocytosed ligands and newly synthesized lysosomal enzymes enroute to lysosome.

Ward HD et al 1987 Biochemistry. 1987 Dec 29, 26(26): 8669-75 identifies and characterizes taglin, a mannose 6-phosphate binding, trypsin-activated lectin from Giardia lamblia.

Zaretzky et al Infect Immun. 1995 Sep; 63(9): 3520-6 teach that Chlamydia trachomatis infection can be blocked by certain sulfated polysaccharides (carrageenan, pentosan polysulfate, fucoidan, and dextran sulfate) and glycosaminoglycans (heparin, heparan sulfate, and dermatan sulfate) but not by other glycosaminoglycans (chondroitin sulfate A or C, keratan sulfate, and hyaluronic acid). The most negatively charged molecules are the most effective at blocking infection. Results of infection at 4 degrees C suggest that sulfated polyanions act by preventing the adherence of chlamydiae to target cells. These and additional blocking studies with enzymes suggest that a heparan sulfate-like glycosaminoglycan on the surface of elementary bodies is involved in the adherence of chlamydiae to target cells.

Zhang JP and Stephens RS Cell. 1992 May 29; 69(5): 861-9.teach that a heparan sulfate-like GAG present on the surface of chlamydia organisms is required for attachment to host cells using purified glycosaminoglycans (GAGs) and specific GAG lyases. Inhibition of attachment following binding of heparan sulfate receptor analogs to chlamydiae and by demonstrating that chlamydiae synthesize a unique heparan sulfate-like GAG. Furthermore, exogenous heparin sulfate, as an adhesion analog, restored attachment and infectivity to organisms that had lost these attributes following treatment with heparin sulfate lyase. This data suggest that GAG adhesion ligand mediates attachment by bridging mutual GAG receptors on the host cell surface and on the chlamydia outer membrane surface.

Zhu et al Proc Natl Acad Sci U S A. 1995 April 11; 92(8): 3546–3550 teach Infection of cells by varicella zoster virus: inhibition of viral entry by mannose 6-phosphate and heparin. Envelope glycoproteins of varicella zoster virus (VZV) contain mannose 6-phosphate (Man6P) residues and Man6P competitively and selectively inhibits infection of cells in vitro by cell-free VZV

Ooij et al. (Infect. Immun. 1997 Vol. 65(2) pp. 758-766) teach a composition comprising monoclonal antibody to mannose-6-phosphate. This antibody binds to C.trachomatis infected cells.

Peterson et (Infect. Immun. Vol. 66(8) pp3848-3855) teach a composition comprising a monoclonal antibody Mab CP-33. This antibody neutralized the infectivity of Chlamydia pneumoniae.

H Boleti et al Journal of Cell Science, Vol 112, Issue 10 1487-1496 1999 investigated the pathway of entry of C. psittaci GPIC and C. trachomatis LGV/L2 into HeLa cells and demonstrated that it does not depend on clathrin coated vesicle formation.

Swanson and Kuo Infect Immun. 1991 Jun, 59(6): 2120-5 teach
Evidence that the major outer membrane protein of Chlamydia trachomatis is glycosylated. The isolated MOMP was shown to bind specifically to concanavalin A, wheat germ agglutinin, and Dolichos biflorus agglutinin in the lectin binding assay. No binding was observed with Ulex europaeus agglutinin, soybean agglutinin, or Ricinus communis agglutinin.

Kuo et al J Clin Invest. 1996 Dec 15, 98(12): 2813-8 teach an N-linked high-mannose type oligosaccharide, expressed at the major outer membrane protein of Chlamydia trachomatis, mediates attachment and infectivity of the microorganism to HeLa cells. The oligosaccharides were released from the glycoprotein by N-glycanase digestion,

Carlson et al Mol Microbiol. 1999 Aug, 33(4): 753-65 teach
Identification and characterization of a Chlamydia trachomatis early operon encoding four novel inclusion membrane proteins. Chlamydia trachomatis is a bacterial obligate intracellular parasite that replicates within a vacuole, termed an inclusion that does not fuse with lysosom. To identify candidate inclusion membrane proteins, antisera were raised against a total membrane fraction purified from C. trachomatis-infected HeLa cells. By indirect immunofluorescence, these antisera recognized the inclusion membrane and, by immunoblot analysis, recognized three Chlamydia-specific antigens of approximate molecular weights 15, 18 and 21 kDa. IncG, encoding an 18 kDa and 21-kDa-doublet Chlamydia antigen, was identified by screening a C. trachomatis, serovar L2, genomic expression library. Three additional genes, incD, incE and incF, were co-transcribed with incG. Monospecific antisera against each of the four genes of this operon demonstrated that the gene products were localized to the Chlamydia inclusion membrane.

Ooij et al teach Infect Immun. 1998 Nov; 66(11): 5364-71 teach
Chlamydia trachomatis resides within a membrane-bound compartment, the inclusion. A distinguishing characteristic of the C. trachomatis life cycle is the fusion of the chlamydia-containing inclusions with each other in the host cell cytoplasm.

Lin et al J Infect Dis. 2000 Mar; 181(3): 1096-100 teach Monocytes-endothelial cell co culture enhances infection of endothelial cells with Chlamydia pneumoniae. The susceptibility of endothelial cells to infection with C. trachomatis and C. psittaci was not enhanced by the monocyte-derived factor(s).

Kuo et al Cell Microbiol. 2002 Microbial Pathogenesis 2002, 32:43-48 teach N-linked high mannose type oligosaccharides competitively inhibit attachment to and infectivity of Chlamydia in HeLa cells. *C. trachomatis* infected mannose-receptor positive cells better than mannose-receptor negative cells. *C. psittaci* infected both mannose-receptor negative and positive cells equally well, while *C. pneumoniae* infected mannose-receptor negative cells better than mannose-receptor positive cells.

16. Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform to the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Right Fax number is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PMR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PMR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Padma Baskar Ph.D., whose telephone number is ((571) 272-0853. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 6.30 a.m. to 4.00 p.m. except First Friday of each bi-week.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. Any inquiry of a general nature

or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Padma Baskar Ph.D.